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Transitioning from NAFLD to MAFLD and MASLD: the toxic relationship with alcohol consumption

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Abstract

Alcohol is a well-known toxic etiologic factor for liver injury. Metabolic substrates of alcohol (especially acetaldehyde) have a major responsibility and genetic susceptibility, alterations in microbiota and immune system are important co-factors for this injury. Major injury in liver is hepatocellular lipid accumulation. Therefore the relationship between non-alcoholic and alcoholic fatty liver diseases should have been defined clearly. Recently two major liver committees adopted new terminologies such as metabolic-associated fatty liver disease (MAFLD), metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction and alcohol-related liver disease (MetALD), and alcoholic liver disease (ALD) instead of non-alcoholic fatty liver disease (NAFLD). These terminologies were based on the effects of metabolic syndrome on liver. Alcohol consumption was defined differently according to these nomenclatures. MAFLD defined alcohol intake (regardless of amount) as "dual etiology fatty liver disease" and the Delphi consensus defined MASLD, MetALD, or ALD according to daily consumption of alcohol amount.

Keywords

Metabolic dysfunction-associated steatotic liver disease, non-alcoholic fatty liver disease, alcoholic liver disease, metabolic dysfunction-associated fatty liver disease, alcohol consumption

Introduction

Non-alcoholic fatty liver disease (NAFLD) has been used for nearly 40 years to describe infiltration of liver parenchyma with fat in patients with no other causes of liver disease or absence of excessive alcohol use. The global prevalence of NAFLD has increased by nearly 50% in the last 30 years. Alcohol use and the risk of developing advanced forms of alcoholic liver disease (ALD) are associated in a dose- and duration-dependent manner. However, there is significant individual heterogeneity due to hereditary variables and the presence of comorbidities. The development of steatosis in ALD is a multifactorial process, including

metabolic changes and alterations in signal transduction pathways. These changes impact not only the breakdown of fat and fatty acids (FAs) but also other aspects of lipid metabolism [1]. A comprehensive understanding of alcohol-induced liver damage requires an understanding of the complex relationship among different hepatic cell types. The primary processes involved in hepatic fibrogenesis encompass the activation of stellate cells and the synthesis of collagen. The resulting fibrosis determines the extent of damage to the liver's structure due to chronic alcohol consumption [2].

Stigmatization of terms like "non-alcoholic" and "fatty" was thought to be a barrier to diagnosis and increased awareness of this disease spectrum. Multi-society committees adopted new terminologies such as metabolic-associated fatty liver disease (MAFLD) in 2020 and metabolic dysfunction-associated steatotic liver disease (MASLD) in 2023 to overcome this problem. Metabolic dysfunction and alcohol-related liver disease (MetALD) is a recently identified type of liver disease that affects individuals with MASLD who consume a specific amount of alcohol. This review aimed to summarize the pathophysiological and clinical effects of alcohol on liver injury.

Alcohol metabolism

Alcohol is known to be a direct hepatotoxin, with its metabolites primarily responsible for this effect. The initial metabolism of ingested alcohol takes place in the gastric mucosa, where multiple isoforms of gastric alcohol dehydrogenase (ADH) facilitate this process. Factors such as gender, age, heredity, and stomach morphology can have an impact on gastric ADH activity [3].

The main metabolism pathway of alcohol is the oxidization of ethanol to acetaldehyde by cytoplasmic ADH. The second pathway involved in ethanol metabolism is the microsomal ethanol-oxidizing system (MEOS) located in the smooth endoplasmic reticulum. This pathway relies on the cytochrome P450 2E1 (CYP2E1) enzyme to convert ethanol into acetaldehyde. As a result of this conversion, reactive oxygen species (ROS) are produced, leading to oxidative stress and inflammation. Under normal physiological conditions, CYP2E1 only converts around 10% of ethanol into acetaldehyde. However, in cases of chronic alcohol consumption, the expression of CYP2E1 is increased, making it more significant in the conversion of ethanol to acetaldehyde. The third pathway is the oxidizing of ethanol to acetaldehyde by heme-containing catalase in the peroxisomes [4].

Exposure to acetaldehyde in alcoholic beverages can result in hazardous symptoms such as hypotension, tachycardia, face flushing, and vomiting. Acetaldehyde disrupts the expression of antioxidant genes, such as nuclear factor erythroid 2-related factor 2 (Nrf-2) and thioredoxin, resulting in reduced synthesis of antioxidant and detoxifying enzymes and decreased activity of the antioxidant defense system [5].

The enzyme aldehyde dehydrogenase (ALDH) is found in the mitochondria of hepatocytes. It catalyzes the oxidation of acetaldehyde to acetate, which is then released into the bloodstream. Acetate is further oxidized to carbon dioxide in other organs outside the liver [6]. Long-term alcohol consumption increases the synthesis of CYP2E1. This leads to higher levels of acetaldehyde, a toxic compound, and reduces the activity of ALDH, an enzyme responsible for breaking down acetaldehyde. As a result, acetaldehyde accumulates in the liver, causing direct damage to the mitochondria and microtubules of liver cells [7]. Elevated acetaldehyde levels may potentially indicate compromised mitochondrial function caused by ethanol-induced mitochondrial depolarization, leading to the autophagic elimination of dysfunctional mitochondria [8]. However, only approximately 20% of individuals with alcohol use disorder progress to develop alcohol-associated hepatitis [1].

Lipolysis in adipose tissue is promoted by acetaldehyde, and FA transporter proteins and FA translocase in the liver absorb increased free FAs. Additionally, acetaldehyde causes the increased expression of lipogenic enzyme genes such as FA synthase, and sterol-CoA desaturase. Ethanol-derived toxic metabolites increase hepatic FA uptake and lipid synthesis and decrease FA oxidation and lipid export. These cause hepatocellular lipid accumulation.

Multiple genome-wide association studies (GWAS) have identified several genetic risk loci for the development of ALD, including the patatin-like phospholipase domain-containing-3 (*PNPLA3*) gene, which is the primary risk factor for the progression of ALD [7]. The rs738409 mutation (C.444 C > G p.Ile148Met) in the *PNPLA3* gene leads to a decrease in hydrolytic activity, causing the accumulation of fat and subsequent liver inflammatory injury [9]. Additionally, the transmembrane 6 superfamily member 2 (TM6SF2) and membrane-bound O-acyltransferase domain-containing protein 7 (MBOAT7), a negative regulator of toll-like receptors (TLRs) signaling in macrophages, play a significant role and are important determinants of ALD progression [7, 10].

Alcohol-induced microbial peptides elevate the concentration of proinflammatory agents in the liver, linked to the epithelial barrier, the protective layer of the mucus membrane, and the gut microbiome. Alcohol directly affects the liver's parenchymal cells, leading to intestinal barrier functioning anomalies, microbiota changes, and enhanced activation of liver cells' TLRs. The modification of gut microbiota has a significant role in the development of liver disorders [11]. Changes in the principal constituents of the human microbiota, including Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, may disrupt normal in vivo functioning, particularly that of the immune system, proliferation of intestinal cells, maintenance of nutrition and cause metabolic disorders such as metabolic syndrome, obesity, and NAFLD [12, 13]. Recent studies indicated that alcohol-producing bacteria can cause fatty liver disease such as high alcohol-producing *Klebsiella pneumonia* (HiAlc *Kpn*) [14]. HiAlc *Kpn* catabolizes carbohydrate substances to produce alcohol and 2,3-butanediol via the 2.3-butanediol fermentation pathway [15]. Additionally, endogenous ethanol produced by HiAlc *Kpn* induces mitochondrial dysfunction in fatty liver disease [16].

Alcohol amounts of different nomenclatures (NAFLD, MAFLD, and MASLD)

The term NAFLD has been used for nearly 40 years to describe infiltration of liver parenchyma with fat in patients with no other causes of liver disease or absence of excessive alcohol use. The prevalence of NAFLD changes according to geographic regions (25.1% in Europe, 44.3% in Latin America) however, the global prevalence was reported as 38%, and it has increased by nearly 50% last 30 years [17].

NAFLD and ALD are the primary causes of chronic liver disease and are linked to significant morbidity and mortality. Alcohol use can synergistically increase the progression of liver disease in persons with viral hepatitis [18]. Alcohol use and the risk of developing advanced forms of ALD are associated in a dose- and duration-dependent manner, although there is significant individual heterogeneity due to hereditary variables and the presence of comorbidities [19]. Nevertheless, the impact of alcohol use on fatty liver disease has been a subject of ongoing controversy. Initial research indicated that moderate alcohol use may have a preventive effect on NAFLD. However, further investigations have revealed that even small amounts of alcohol consumption can increase the risk of disease progression [20].

Stigmatization of terms like "non-alcoholic" and "fatty" was thought to be a barrier to diagnosis and increased awareness of this disease spectrum. Therefore, multi-society committees adopted new terminologies such as MAFLD in 2020 [21] and MASLD in 2023 [22] to overcome this problem.

Beverages and drinking patterns

A "standard drink" refers to a volume of alcoholic beverage that includes a consistent amount of ethanol, measured in grams, regardless of the type of beverage. In the United Kingdom, the term "unit" refers to a quantity of an alcoholic beverage that includes around 8–9 grams of ethanol. In North American literature, the term "a drink" is used to describe a quantity of an alcoholic beverage that contains about 12 grams of ethanol. The quantities of alcohol selected to represent a typical drink may vary in different nations, depending on local traditions and how beverages are packaged [2]. According to the US Department of Health and Human Services, one standard drink means a beverage containing approximately 14 g (0.6 fluid ounces) of pure ethanol (i.e., alcohol), corresponding to 12 fluid ounces of regular beer (5% alcohol), five ounces of wine (12% alcohol), or 1.5 ounces of 80 proof distilled spirits (40% alcohol) [23]. International guidelines and consensuses reported different amounts of alcohol intake to define light or moderate drinking (Table 1).

Table 1. The suggestions of international societies on alcohol amount of light or moderate drinking

Society	Alcohol amount for men	Alcohol amount for women
AASLD, 2020 [38]	< 21 drinks/week	< 14 drinks/week
AISF, 2020 [39]	< 2 drinks/day	< 1 drinks/day
NICE, 2022 [40]	< 30 g/day	< 20 g/day
Asia-Pacific group, 2017 [41]	< 14 drinks/week	< 7 drinks/week
NIAAA, 2016 [24]	< 2 drinks/day	< 1 drinks/day
Multi-Society Delphi Consensus, 2020 [21]	< 30 g/day	< 20 g/day
ACG, 2024 [25]	< 21 drinks/week	< 14 drinks/week
EASL, EASD, and EASO 2024 [42]	< 30 g/day	< 20 g/day

AASLD: American Association for the Study of Liver Disease; ACG: American College of Gastroenterology; AISF: Italian Association for the Study of the Liver; EASD: European Association for the Study of Diabetes; EASL: European Association for the Study of the Liver; EASO: European Association for the Study of Obesity; NIAAA: National Institute on Alcohol Abuse and Alcoholism; NICE: National Institute for Health and Care Excellence

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines "heavy alcohol use" as consuming 4 or more drinks per day, or 14 or more drinks per week for men, and 3 or more drinks per day, or 7 or more drinks per week for women [24]. According to the American College of Gastroenterology guideline, "harmful drinking" is indicated by consuming 3 or more drinks per day, or 21 or more drinks per week for men, and 2 or more drinks per day, or 14 or more drinks per week for women [25].

Recent studies have shown that "binge drinking" is linked to negative alcohol-related outcomes. According to the NIAAA, binge drinking is defined as consuming enough alcohol to reach a blood alcohol concentration of 0.08% (0.08 g/dL), which translates to 5 drinks for men and 4 drinks for women within 2 hours. Additionally, consuming twice the threshold for binge drinking is referred to as "high-intensity drinking" [24]. Binge drinking was found to be linked to an increased risk of liver disease, regardless of average alcohol use and confounding variables [26]. Additionally, binge drinking was associated with increased all-cause mortality, liver-related mortality, and liver-related events [27]. Binge drinking and high-intensity drinking were related to augmentation of liver injury such as ALD, NAFLD, hepatitis B virus (HBV), hepatitis C virus (HCV), and autoimmune liver diseases [28].

The level of alcohol consumption has a direct impact on liver damage, with the type of alcoholic beverage and the timing of alcohol intake concerning meals also playing a role. Research suggests that consuming wine or beer is less correlated with alcohol-related liver disease compared to drinking liquor. Furthermore, the risk of developing cirrhosis is lower when alcohol is consumed with meals as opposed to without [29, 30].

Differences between alcohol-related liver disease and NAFLD

Distinguishing between alcohol-related liver disease and NAFLD is difficult in people who have both conditions and consume alcohol, as these two diseases have remarkably comparable histological and molecular biology characteristics at every stage of the illness. The differentiation between the two disorders must be established based on clinical criteria, biochemical examinations, and a record of alcohol use (Table 2). Therefore, NAFLD is a diagnosis that is made by excluding other possible causes and confirming the absence of considerable alcohol usage [20].

Table 2. The alcohol amounts of fatty liver terms (NAFLD, MAFLD, SLD)

Alcohol amount	NAFLD	MAFLD	SLD
< 30 g/day for men; < 20 g/day for women	NAFLD	Dual etiology of fatty liver disease	MASLD
30–60 g/day for men; 20–50 g/day for women	AFLD	Dual etiology of fatty liver disease	MetALD
> 60 g/day for men; > 50 g/day for women	AFLD	Dual etiology of fatty liver disease	ALD

ALD: alcoholic liver disease; MAFLD: metabolic-associated fatty liver disease; MASLD: metabolic dysfunction-associated steatotic liver disease; MetALD: metabolic dysfunction and alcohol-related liver disease; NAFLD: non-alcoholic fatty liver disease

The risk of severe ALD increases in men if they consume more than 60–80 g of alcohol per day for ten years. On the other hand, women are at an elevated risk of developing the same level of liver injury by drinking 20–40 g of alcohol per day [1]. Chronic alcohol intake leads to a variety of liver abnormalities. Steatosis, often known as fatty liver, is the initial and predominant reaction that occurs in over 90 percent of individuals who take 4–5 regular alcoholic beverages daily. Prolonged alcohol consumption can lead to the progression of alcohol-induced liver disease, resulting in liver inflammation (steatohepatitis), fibrosis, cirrhosis, and perhaps liver cancer (hepatocellular carcinoma) [31].

Differences between NAFLD and MAFLD

NAFLD is a diagnosis that applies to patients who have fatty liver that is not attributed to alcohol, viral infection, or other conditions. In other words, NAFLD can be diagnosed regardless of the underlying cause of the fatty liver, making the patient population a very heterogeneous group. For NAFLD diagnosis, the daily alcohol consumption cut-off was < 30 g for men and < 20 g for women (Table 2). A group of hepatologists proposed the MAFLD term in 2020 [21]. For MAFLD diagnosis, patients with hepatic steatosis should have one of the following metabolic conditions: 1) overweight or obesity, 2) type 2 diabetes, and 3) 2 or more metabolic risk factors: elevated waist circumference (≥ 102 cm for male, ≥ 88 cm for female), body mass index (BMI) ≥ 25 kg/m^2, glucose ≥ 110 mg/dL, triglycerides ≥ 150 mg/dL, lower high-density lipoprotein (HDL) levels (< 50 mg/dL for male, < 40 mg/dL for female), blood pressure ≥ 130 or ≥ 85, prediabetes, homeostasis model assessment of insulin resistance (HOMA-IR) ≥ 2.5. However, there was no limitation on alcohol consumption and concomitant liver diseases in diagnosing the MAFLD. It was stated that light or moderate alcohol consumption has debate on the prognosis of liver steatosis. In the case of co-existence with MAFLD and alcohol intake, the definition of "dual etiology fatty liver disease" is recommended.

In a recent study, the authors evaluated new markers for alcohol consumption and sought to examine the role of MAFLD in alcohol consumption by reclassifying retrospective data based on the new MAFLD criteria. The study reported that among 184 patients, 28.6%, 28.5%, and 25% were found to have moderate (≥ 10 g < 60 g ethanol/day) to excessive (≥ 60 g ethanol/day) alcohol consumption in NAFLD, ALD, and MAFLD, respectively [32].

Difference between MAFLD, MASLD, and MetALD

MASLD replaces the previous term NAFLD and is included in the definition of SLD. In addition to MASLD, SLD encompasses ALD, MetALD, which defines MASLD with alcohol intake, specific etiologies of SLD (such as drug-induced and monogenic disorders), and cryptogenic SLD.

Hepatic steatosis, also known as fatty liver, is a complex condition influenced by a myriad of factors, including obesity, cardiometabolic disturbances, and alcohol consumption. In 2023, a multi-society Delphi consensus statement proposed a shift in the nomenclature from NAFLD to MASLD [22]. This change emphasizes the central role of metabolic dysfunction in the pathogenesis of hepatic steatosis and aims to reduce the stigma associated with the condition. Traditionally, NAFLD was defined as a "diagnosis of exclusion" in patients with SLD who did not consume "significant amounts of alcohol"—defined as more than 21 standard drinks per week (294 g) for men and more than 14 standard drinks per week (196 g) for women. However, emerging evidence suggests that even moderate alcohol consumption, exceeding one drink per day for women and two drinks per day for men, can increase the risk of advanced liver disease, which could be slightly against the MetALD concept [33].

The diagnosis of MASLD requires the presence of hepatic steatosis together with at least one cardiometabolic risk factor (CMRF). These risk factors include a BMI of 25 kg/m^2 or above, an enlarged waist circumference, diabetes, hypertension, elevated triglyceride levels, low levels of HDL, and up to moderate alcohol intake [< 20 mg/day (140 g/week) for women, < 30 mg/day (210 g/week) for men]. The multi-society Delphi consensus statement highlighted that alcohol, in conjunction with CMRF, is a significant cause of steatosis [34].

MetALD is a recently identified type of liver disease that affects individuals with MASLD who consume a specific amount of alcohol (Table 2). In females, MetALD is diagnosed when they drink between 140 and 350 grams of ethanol per week, while in males, the diagnosis is made when they consume between 210 and 420 grams of ethanol per week [34]. There are subgroups of MetALD according to average daily or weekly alcohol intake. It was stated that alcohol intake was a continuum and recommended terms were "MASLD predominant" to define average alcohol intake near 20 mg/day (140 g/week) for women, 30 mg/day (210 g/week) for men, and "ALD predominant" to define average alcohol intake near 50 mg/day (350 g/week) for women, 60 mg/day (420 g/week) for men [22].

There are multiple studies on alcohol's effect on the liver (Table 3). The inconsistent results can be attributed to several factors. Firstly, most of the studies used a cross-sectional design, which may not accurately capture the long-term effects of the studied variables. Additionally, few liver-related events were observed in the longitudinal observations, which limits the ability to draw definitive conclusions. Furthermore, there was variation in the instruments used to diagnose NAFLD, as well as differing definitions of "alcoholic unit" (ranging from 8 to 12 grams each). The selection criteria for participants also varied due to the different guidelines applied. Moreover, there was an incomplete adjustment for confounding factors, such as lifestyle factors, which may have influenced the results. Finally, there was a primary focus on current alcohol consumption, potentially neglecting other important factors such as prior consumption [35].

Table 3. The studies on alcohol's effects on liver

Author, year	Study design	Number of patients	Alcohol amount and duration	Conclusion
Roerecke et al, 2019 [19]	Systematic review and meta-analysis	2.5 million participants, 5,500 cirrhosis	> 1 drinks/day for women; ≥ 5 drinks/day for men	The risk increased beyond consumption of one drink or more per day. However, risks varied widely and the analysis of case-control studies showed no risk increase for consumption of 1–4 drinks/day
Simpson et al, 2019 [30]	Prospective cohort study	401,806 middle-aged female	≥ 15 drinks/week (mean 220 g alcohol)	Cirrhosis incidence increases with total alcohol intake, even at moderate levels of consumption
Sinn et al, 2022 [43]	Nationwide cohort study	367,612 patients without liver disease	< 40 g/day for women, < 60 g/day for men	Small amounts of alcohol intake were associated with increased liver-related and all-cause mortality among individuals with elevated ALT levels
Mitchell et al, 2018 [44]	Case-control	187 biopsy-proven NAFLD	< 70 g/week	Modest (1–70 g/week) alcohol consumption, particularly wine in a non-binge pattern, is associated with lower fibrosis in patients with NAFLD
Ferri et al, 2022 [45]	Case-control	276 patients with NAFLD (alcohol consumption up to 140 g/week for women; 210 g/week for men)	< 70 g/week	Very low alcohol usage is associated with a lower prevelance of cirrhosis and HCC in patients with NAFLD
Llamosas-Falcón et al, 2024 [46]	Systematic review and meta-analysis	5 million participants, 15,150 liver cirrhosis	> 25 g/day	Alcohol consumption over 25 g/day is associated with higher morbidity and mortality rates in liver cirrhosis. Additionally, this relation is positively correlated with alcohol amount per day
Åberg et al, 2020 [47]	Follow-up cohort	8,345 patients with hepatic steatosis	10–19 g/day	Doubled the risk for advanced liver disease compared to lifetime abstainers. 0–9 g/day intake is associated with 21% all-cause mortality risk reduction
Zhu et al, 2024 [33]	Retrospective cohort	2,630 patients with MAFLD	≥ 8 drinks/week for women and ≥ 15 drinks/week for men	Higher weekly alcohol consumption was significantly associated with all-cause and cause-specific mortality. > 2 drinks/week is associated with all-cause mortality
Israelsen et al, 2024 [34]	Prospective cohort	446 patients with excessive alcohol intake	> 24 g/day for women and > 36 g/day for men	The risk of decompensation increased in a stepwise manner from MASLD, through Met ALD, to ALD

ALD: alcoholic liver disease; ALT: alanine transaminase; HCC: hepatocellular carcinoma; MAFLD: metabolic-associated fatty liver disease; MASLD: metabolic dysfunction-associated steatotic liver disease; MetALD: metabolic dysfunction and alcohol-related liver disease; NAFLD: non-alcoholic fatty liver disease

Multiple studies found that those with fatty livers who consume low to moderate amounts of alcohol have a lower chance of developing severe liver disease compared to those who do not drink alcohol at all [35, 36]. In a study that involved a population of 6,700 individuals and extended 12 years, individuals who had diabetes and consumed significant amounts of alcohol had a 20-fold greater risk of developing liver cancer, being admitted to the hospital due to liver disease, or mortality from liver-related causes, compared to those who consume little to no alcohol and do not have diabetes [37].

The low reliability of threshold values for alcohol use, and therefore the lack of standardization of definitions such as social drinking and binge drinking, are insufficient to provide information about actual alcohol use. However, it is not clear whether the effect of low to moderate alcohol intake is harmful or harmless for liver and nearly one-fourth of patients with MAFLD have reported to have moderate alcohol intake [32]. Therefore instead of separating the alcohol and metabolic patterns using an umbrella term including all disorders that cause steatosis in liver such as "SLD" can be favorable.

Conclusions

NAFLD and ALD are significant contributors to chronic liver disease, leading to considerable morbidity and mortality. The use of alcohol can exacerbate the progression of liver disease in individuals with viral hepatitis. There has been ongoing debate about the impact of alcohol use on fatty liver disease, leading to the introduction of new terms such as MAFLD and MASLD. However, the effect of changes in alcohol consumption on the development of MAFLD is not yet clear.

Conversely, the updated definitions of SLD incorporate specific criteria for MASLD and MetALD, based on CMR and alcohol consumption. Given the ongoing discussions, the current circumstances require us to move past defining the disease and instead concentrate on the specific actions required to enhance the outcomes of SLD management.

Abbreviations

ADH: alcohol dehydrogenase

ALD: alcoholic liver disease

ALDH: aldehyde dehydrogenase

BMI: body mass index

CMRF: cardiometabolic risk factor

CYP2E1: cytochrome P450 2E1

FAs: fatty acids

HDL: high-density lipoprotein

HiAlc *Kpn*: high alcohol-producing *Klebsiella pneumonia*

MAFLD: metabolic-associated fatty liver disease

MASLD: metabolic dysfunction-associated steatotic liver disease

MetALD: metabolic dysfunction and alcohol-related liver disease

NAFLD: non-alcoholic fatty liver disease

NIAAA: National Institute on Alcohol Abuse and Alcoholism

PNPLA3: patatin-like phospholipase domain-containing-3

TLRs: toll-like receptors

Declarations

Author contributions

MO: Writing—review & editing. AT: Writing—review & editing, Supervision. MEK: Conceptualization, Investigation. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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